I. Indication(s) for use:

ONTAK is indicated for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor.

II. Dosage form, route of administration and recommended dosage:

ONTAK is supplied in single use vials as a sterile, frozen solution intended for intravenous (IV) administration. Each 2 mL vial of ONTAK contains 300 mcg of recombinant denileukin diftitox in a sterile solution of citric acid (20 mM), EDTA (0.05 mM) and polysorbate 20 (<1%) in Water for Injection, USP. The solution has a pH of 6.9 to 7.2.

ONTAK is for intravenous (IV) use only. The recommended treatment regimen (one treatment cycle) is 9 or 18 mcg/kg/day administered intravenously for five consecutive days every 2 1 days. ONTAK should be infused over at least 15 minutes.

III. Manufacturing and Controls

A. Manufacturing and Controls

ONTAK (denileukin diftitox, $DAB_{389}IL\text{-}2$) is a fusion protein, consisting of a fragment of diphtheria toxin genetically fused to Interleukin-2.

The manufacturing process is broken down into — major operations. Fermentation and primary recovery is a multi-step — process. The batch fermentation is comprised of an -- phase followed by an ——— phase of ——— Cells are harvested by ——— and — Following — an ——— is prepared by ——— This — is ———

T h e ------- are ——— and the $DAB_{389}IL\text{-}2$ purified by reverse-phase chromatography. The $DAB_{389}IL\text{-}2$ is eluted from a ——— ——— using an ———

Using a multi-step diafiltration technique, the denatured $DAB_{389}IL\text{-}2$ is ——— While in'this solution the $DAB_{389}IL\text{-}2$ is renatured into a biologically active conformation.

The resulting Purified Drug Substance is diluted to a concentration of ——— , formulated and frozen at ———

Purified Drug Substance is shipped frozen to _____ where it is thawed and the final steps for filling are completed. Quality Control testing of Final Drug Product occurs at _____ and at Seragen, Inc. through contract relationships.

Purified Drug Substance Specifications

Test	Specification
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	Conforms to reference
_____	Conforms to reference
_____	Conforms to reference
_____	Conform to reference
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

Final Drug Product Specifications

Test	Product Specifications
[redacted]	
[redacted]	Conforms to Reference
[redacted]	
[redacted]	Conforms to Reference
pH	6.9 to 7.2
Citrate Concentration	[redacted]
EDTA Concentration -------	
Polysorbate 20 Concentration	< 1.0%
Color and Appearance	Clear/No Particulates
Sterility	Sterile
General Safety	Survival Both Species
Particulates	Pass

B. Stability Studies

Purified Drug Substance Stability at [redacted]

No meaningful change in stability indicating parameters was observed when Purified Drug Substance is stored at [redacted] for at least 36 months; studies are ongoing.

Final Drug Product [redacted] or Nominal [redacted] Stability

No meaningful change in stability indicating parameters was observed when Final Drug Product was stored at nominal [redacted] or nominal [redacted] for at least 36 months; studies are ongoing.

Final Drug Product Nominal - 10°C Stability

A decrease in stability indicating parameters was observed when Final Drug Product was stored over time at nominal -10°C; results remained within product expiration specifications for at least 15 months.

Expiration Dating Analysis

Expiration dating analysis was performed on data generated from the shelf-life stability studies on the three process consistency lots.

Expiration dating analysis indicates that $DAB_{389}IL-2$ Final Drug Product is stable for a minimum of 24 months when stored at or below nominal -26°C. The expiration dating period for $DAB_{389}IL-2$ Final Drug Product, stored at nominal -10°C, was set conservatively at 12 months.

The original expiration dating analysis was corroborated and expanded in a real-time stability study. This final stability study evaluated three lots of Final Drug Product. Following 28 to 30 months storage at -26°C (depending on the lot), Final Drug Product lots were transferred to -10°C storage. Samples were tested every three months using stability indicating assays. The data confirmed that product which has been stored at -26°C for up to 30 months remains within the expiration specifications when transferred to -10°C for 12 months.

C. Validation

A Validation Master Plan defines the validation program implemented at all Seragen manufacturing facilities. This Validation Master Plan addresses the validation programs for the utilities, equipment, analytical methods, computers or processes that are part of the normal operation of the Quality Control and Manufacturing departments.

The Validation Master Plan includes:

- Definition of the parties responsible for the various validation functions
- Identification of the systems and subsystems validated
- General acceptance criteria for each of the systems and subsystems
- Computer System Validation Requirements
- Process Validation Requirements
- Cleaning Validation Requirements
- Assay Validation Requirements

Each of these validation programs was implemented using individual protocols which employed predetermined acceptance criteria. Each of these individual protocols was reviewed and approved by the Quality Assurance unit.

D. Labeling

At the recommendation of the USAN Council, Denileukin Diftitox has been adopted as the non-proprietary name for $DAB_{389}IL\text{-}2$. A more structurally descriptive name for $DAB_{389}IL\text{-}2$ is [diphtheria fragment A and B (Met_1-Thr_{387})-His-Interleukin-2 (Ala_1-Thr_{133})]. The trade name for denileukin diftitox is ONTAK®. The trade name is not in conflict with a name of any other product.

ONTAK is supplied as a 150 mcg/mL sterile, frozen solution (300 mcg in 2 mL) in a sterile, single-use vial, NDC 64365-503-01, 6 vials in a package. The expiration period for ONTAK is 12 months at or below -10°C. Store frozen at or below -lOoC.

E. Establishment Inspection

Inspections of Seragen's bulk manufacturing contract facility, Marathon Biopharmaceuticals, LLC, and contract filling facility _____ were conducted on April 27 through May 1, 1998 and April 22 through 24, 1998, respectively.